Pulmonary nocardiosis re-visited: experience of 35 patients at diagnosis

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Abstract Pulmonary infection by *Nocardia* is an uncommon opportunistic infection in humans. Thirty-five patients with pulmonary nocardiosis were identified in two tertiary referral hospitals. A retrospective review of the patient characteristics, clinical and laboratory features including antimicrobial susceptibility at diagnosis was carried out. Radiological features derived from chest radiographs and CT scans were also documented. In our population, the predominant risk factors were immuno-compromised state, corticosteroid therapy, and underlying pulmonary pathology. The presenting features were similar to those previously described but disseminated infection was not common. The radiological changes were diverse and non-specific. *Nocardia asteroides* was the commonest species. Most *Nocardia* isolates were susceptible to imipenem, ceftriaxone, amikacin, and cotrimoxazole. Co-existing microbial agents are common and reflect the underlying complex disorders.

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INTRODUCTION

Nocardia species are Gram-positive, branching, filamentous aerobic bacteria. Potentially pathogenic strains of *Nocardia* to humans are found in soils and cause cutaneous syndromes such as mycetomas or systemic infections. Opportunistic systemic infections are uncommon but well recognised especially in immuno-compromised hosts including acquired immune deficiency syndrome (AIDS) patients. Pulmonary nocardiosis is perhaps the most significant and may also spread by the haematogenous route to a wide range of organs including the brain.

We have retrospectively reviewed 35 patients with pulmonary nocardiosis diagnosed in two tertiary referral hospitals in the last 5 years. We report here on the clinical, microbiological and radiological features at diagnosis. To our knowledge, this represents the largest series of patients with pulmonary nocardiosis in the literature.

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METHODS

A search was conducted via the microbiology laboratory databases of two tertiary referral hospitals that serve a state population of around 1.5 million people. Patients with at least one positive sputum or respiratory specimen (from bronchoscopic lavage or washings, endotracheal tube aspirates or lung biopsies) for *Nocardia* species were identified in the 5-year period from December 1995 to December 2000. A retrospective review of their case notes, laboratory results including microbiological investigations was carried out. The corresponding radiological investigations were reviewed by two radiologists (VA, JS).

Microbiological identification of Nocardiae

All respiratory specimens were examined by Gram stain. Where microscopy indicated the presence of branching, beaded, filamentous Gram-positive bacilli, or colonies suggestive of *Nocardia* grew on the standard plates extended cultures were performed. In addition to routine culture, blood agar, blood agar with nalidixic acid-colistin and Lowenstein-Jensen + glycerol and charcoal yeast agar were set up and incubated for a minimum of 7 days

at 35°C in a CO_2 -enhanced environment. Genus identification of *Nocardia* was based upon appearance under Gram stain, staining with the modified Ziehl–Neelsen technique and colony morphology (a white creamy yellow colony with powdery surface). Species identification was usually performed by sequencing of the 16S ribosomal RNA gene and comparison of the sequence obtained with the genetic database Genbank® (National Center of Biotechnology Information, NIH, Bethesda, Maryland, USA). Sequence homology of greater than 99% was considered as definite identification. Sensitivity testing to a panel of antibiotics was performed by the Kirby-Bauer disc diffusion method as described for *Nocardia* isolates (1).

Definitions

Co-existence of other microbial pathogens was defined by a positive culture from either the same respiratory specimen or another specimen within 7 days of detection of pulmonary nocardiosis. The significance of identification of *Nocardia* was arbitrarily defined as the clinical decision to institute anti-*Nocardia* therapy or as assessed by microbiologists at the time of management.

RESULTS

Patient characteristics

Thirty-five patients with *Nocardia* recovered from respiratory specimens were identified in the 5-year period, which represents an annual incidence of at least 4.7 per million. Patients comprised 21 men and 14 women (male to female ratio 1.5:1) with a median age of 65 years (range 25–90) at diagnosis.

Table 1 shows the underlying diseases and relevant treatment histories of these patients. The majority (22/35 or 63%) of them had an underlying respiratory disorder ranging from common conditions such as chronic obstructive airway disease (COAD), asthma and bronchiectasis to less common ones such as previous tuberculosis and cystic fibrosis. Multiple co-existing respiratory pathology was not unusual. The non-respiratory disorders comprised patients with underlying haemopoietic or non-haematological malignancies, solid organ or marrow transplantation, autoimmune disorders, and non-malignant CD4 lymphopenia including one HIV positive patient. Among all patients, 21 (60%) were receiving corticosteroids and/or other forms of immuno-suppressive therapy. Therefore, in this population, almost all of our patients (33/35 or 94%) with pulmonary nocardiosis had an underlying respiratory pathology and/or were 'immuno-compromised' as a result of their underlying diseases or treatment. Nevertheless, there were exceptions, with two previously healthy patients (cases 34 and 35) being noted. Furthermore, there did not seem to have an obvious relationship with smoking history (29%), diabetes mellitus (28%) or particular occupations.

Clinical and laboratory features

Table 2 summarises the presenting clinical features and laboratory investigations of the patients. Respiratory symptoms (cough and shortness of breath) were frequently present. There was no consistent description of the sputum colour when this was a prominent symptom. Fever and systemic symptoms were also common. Pleuritic chest pain was noted in nearly one-third of patients. The case records did not allow an accurate appraisal of the interval between the onset of symptoms and the diagnosis but a delay of 5 months was documented in one of the cases.

A mild leucocytosis with neutrophilia (mean neutrophil count 10.6×10^9/l, range $3.3–23.5 \times 10^9$/l) and an elevated C-reactive protein (mean level 108 mg/l, range 11–230 mg/l) were noted. Data on changes in arterial blood gases or lung function studies prior to diagnosis were insufficient to allow meaningful analysis.

Sputum samples were able to provide the microbiological diagnosis in nearly half of the patients, whilst bronchoscopic procedures allowed the diagnosis to be made in an additional two-fifths. However, a targeted procedure such as CT-guided fine needle aspiration or lung biopsy was required in five patients.

Lung biopsies were available in four patients, revealing typical acute necrotising pneumonia with abscess (Fig. 1) or non-specific inflammation with fibrosis. Histopathologically, only one of the four specimens allowed ready identification of the organism with methenamine silver stains.

Disseminated systemic nocardiosis beyond the lungs was actively sought (by at least a CT or MRI of the brain) in 11 patients. Three patients (8.5% overall) had haematogenous spread of nocardiosis: the scapula in one, the brain and nocardial bacteraemia in another, and multiple sites in the other patient.

Radiological features

Radiological examinations at diagnosis were available for review in 23 patients and results are shown in Table 3.

All 22 patients with chest radiographs available for review were abnormal. The commonest abnormality was non-segmental air-space consolidation (68%) and not uncommonly involving multiple areas. Pulmonary nodule(s) was the next most common manifestation found in 55%—solitary pulmonary nodules (SPN) being slightly more frequent than multiple nodules. Cavitation was seen in one of seven patients with SPNs and two (including case 26) of the five patients with multiple nodules.

Table I. Underlying diseases and relevant treatment histories of patients with pulmonary nocardiosis.

Case	Sex/age	Underlying diseases	Relevant treatment history
1	F71	COAD	Prednisolone 5 mg daily for years
2	M90	COAD	—
3	F77	COAD/asthma, bronchiectasis	Prednisolone 15 mg daily, home oxygen
4	M68	COAD/asthma; bronchopulmonary aspergillosis	Prednisolone ceased 2 months prior
5	M53	COAD/asthma; bronchopulmonary aspergillosis	Prednisolone 25 mg daily for non-respiratory indication
6	M71	COAD; primary pulmonary fibrosis	Prednisolone 50 mg daily; home oxygen
7	F72	COAD; bronchiectasis; cyclical neutropenia	Prednisolone 7.5 mg daily; granulocyte-colony-stimulating factor 3 × every 2 weeks
8	M81	COAD; interstitial lung disease with fibrosis; adenocarcinoma of the lung	Radiotherapy to lung; home oxygen, prednisolone
9	M64	COAD; metastatic adenocarcinoma of colon to lung and bones	Dexamethasone for palliation
10	M54	Asthma; allergic bronchopulmonary aspergillosis	Prednisolone 5 mg daily for years
11	F71	Asthma; bronchiectasis; previous *Mycobacterium avium-intracellulare* infection	Prednisolone 12.5 mg daily
12	F48	Asthma; bronchiectasis	—
13	M75	Asthma; obstructive sleep apnea	Home oxygen
14	F77	Late onset bronchiectasis	—
15	M41	Cystic fibrosis with bronchiectasis, sinusitis	Prophylactic antibiotic
16	F86	Previous pulmonary tuberculosis with lobectomy and thoracoplasty	—
17	M57	Wegener's granulomatosis; asthma; bronchiectasis	Prednisolone 50 mg + cyclophosphamide 100 mg daily
18	M74	Poorly differentiated small cell lung cancer with scalp and lung secondaries	—
19	M72	Bronchiectasis; Waldenstrom's macroglobulinemia	Chlorambucil and Prednisolone for years then cyclophosphamide
20	M72	Asthma; Kyphoscoliosis; chronic lymphatic leukemia for years	—
21	M58	Relapsed advanced non-Hodgkin's lymphoma	Prednisolone + vincristine; abdominal radiotherapy; Previous combination chemotherapy
22	M58	Hodgkin's disease, previous autologous marrow transplant, complicated by probable autologous hepatic graft vs. host disease	Prednisolone 100 mg daily + cyclosporin A 150 mg Bd
23	M62	Angioimmunoblastic lymphadenopathy with transformation to lymphoma; COAD	Prednisolone for months then combination CHOP chemotherapy
24	F30	Acute myeloid leukaemia post second allogeneic marrow transplant with grade IV graft vs. host disease	Antithymocyte globulin, methylprednisolone, mycophenolate, antiinterleukin-2 receptor (anti-T-lymphocyte) antibodies, and Intravenous immunoglobulins
25	F48	Possible idiopathic CD4 lymphopenia, blood CD4 count: 130/μl	—
26	M40	HIV infection diagnosed at same admission, blood CD4 count: 32/μl; alcoholic; Hepatitis C	—
27	F84	Disseminated ovarian cancer diagnosed at same admission	—
28	M34	Glioblastoma multiforme of the brain	Post-operative cranial radiotherapy, chemotherapy; dexamethasone 8 mg daily
29	F62	Renal transplant for IgA nephropathy	Prednisolone 15 mg + cyclosporin A + mycophenolate
30	F25	Renal transplant then combined renal and pancreatic transplant 2 years later. Complicated by (i) post-transplant lympho-proliferative disease of pancreas and kidney; (ii) renal vein thrombosis on haemodialysis	—

Table 1. *Continued*

Case	Sex/age	Underlying diseases	Relevant treatment history
31	M39	Heart-lung transplant 1994 for severe steroid-dependent asthma and bronchiectasis and dilated cardiomyopathy. Complicated by MAI, aspergillosis, CMV colitis, pseudomonas, bronchiolitis obliterans	Prednislone 10 mg daily + tacrolimus 4mg Bd + azathioprine 150 mg daily; Previous Anti-thymocyte globulin and methylprednisolone
32	M65	Microscopic polyarteritis nodosa with chronic renal failure	Prednisolone 80 mg + cyclophosphamide 50 mg daily
33	M40	Nil (Refractory cluster headache)	Prednisolone 75 mg daily
34	F77	Nil (spinal stenosis)	—
35	F74	Nil	—

Abbreviations: COAD = chronic obstructive airway disease; MAI = *mycobacterium avium-intracellulare*; CMV = cytomegalovirus; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisolone

Table 2. Presenting symptoms and laboratory features of patients with pulmonary nocardiosis.*

Cough	57%	
Shortness of breath	50%	
Fever	36%	
Sputum	32%	
Chest pain	29%	
Anorexia and loss of weight	21%	
Haemoptysis	7%	
Confusion	7%	
Disseminated infection	8.5%	
Scapular mass	(1)	
Brain and nocardial bacteraemia	(1)	
Retina, skin, and para-spinal mass	(1)	
Mean white cell count at diagnosis	12.7×10^9/l	
Mean absolute neutrophil count	10.6×10^9/l	
Mean C-reactive protein	108 mg/l	
The yield of various diagnostic specimens		
sputum	47%	(16)
BAL	44%	(15)
Endotracheal tube aspirate		(1)
CT chest-guided fine needle aspiration }	14%	(4)
Video-assisted thoracoscopic lung biopsy}		(1)

*Number in parentheses.

Pleural effusion and lobar consolidation were uncommonly observed (18%).

On 11 CT scans of the chest, pulmonary nodules, either solitary or multiple, were seen in 64%, with three of seven showing cavitation. These nodules were of moderate size ranging from 1 to 3 cm. An irregular mass of more than 3 cm was seen in one case. Non-segmental air-space consolidation was seen in 55%, with lesions frequently abutting the pleural surfaces, and occasionally extending to the chest wall. A mixed pattern of consolidation and pulmonary nodules was often apparent. Pleural effusion was detected in 36%. Lobar consolidation or ground-glass opacities were uncommon. Nevertheless, ground-glass opacity was the only abnormality noted in one patient.

There was no zonal preference of involvement shown by either chest radiography or CT. The spectrum of radiological manifestations is illustrated in Fig. 2.

Microbiological features

Table 4 shows the species identification of the *Nocardia* isolates among these patients. *N. asteroides* accounts for 60% of all the nocardiae successfully identified. This was followed by *N. nova, N. farcinica* and *N. transvalensis* while the other species such as *N. brasiliensis* were less common.

Table 5 shows the antimicrobial sensitivity patterns that were available in 22 isolates. Susceptibility *in vitro* to cotrimoxazole was found in 80%, compared to 90% susceptibility to imipenem. Ceftriaxone and amikacin appeared to have significant *in vitro* activity against *Nocardia*, although the number studied was limited. On the contrary, other aminoglycosides, the tetracycline group, erythromycin, quinolone (ciprofloxacin), and ampicillin had *in vitro* activity against less than 50% of the isolates tested. Antimicrobial sensitivity of *Nocardia* spp may assist with species identification as characteristic patterns may occur. For example, *N. nova* is the only group sensitive to erythromycin and *N. farcinica* is cefotaxime resistant.

Recovery of additional organisms simultaneously or temporally close to the positive specimens for *Nocardia* was very common in our patient group (21/35 or 60%). Multiple microbial agents (more than two) were present in eight cases. Table 6 shows the frequency of the

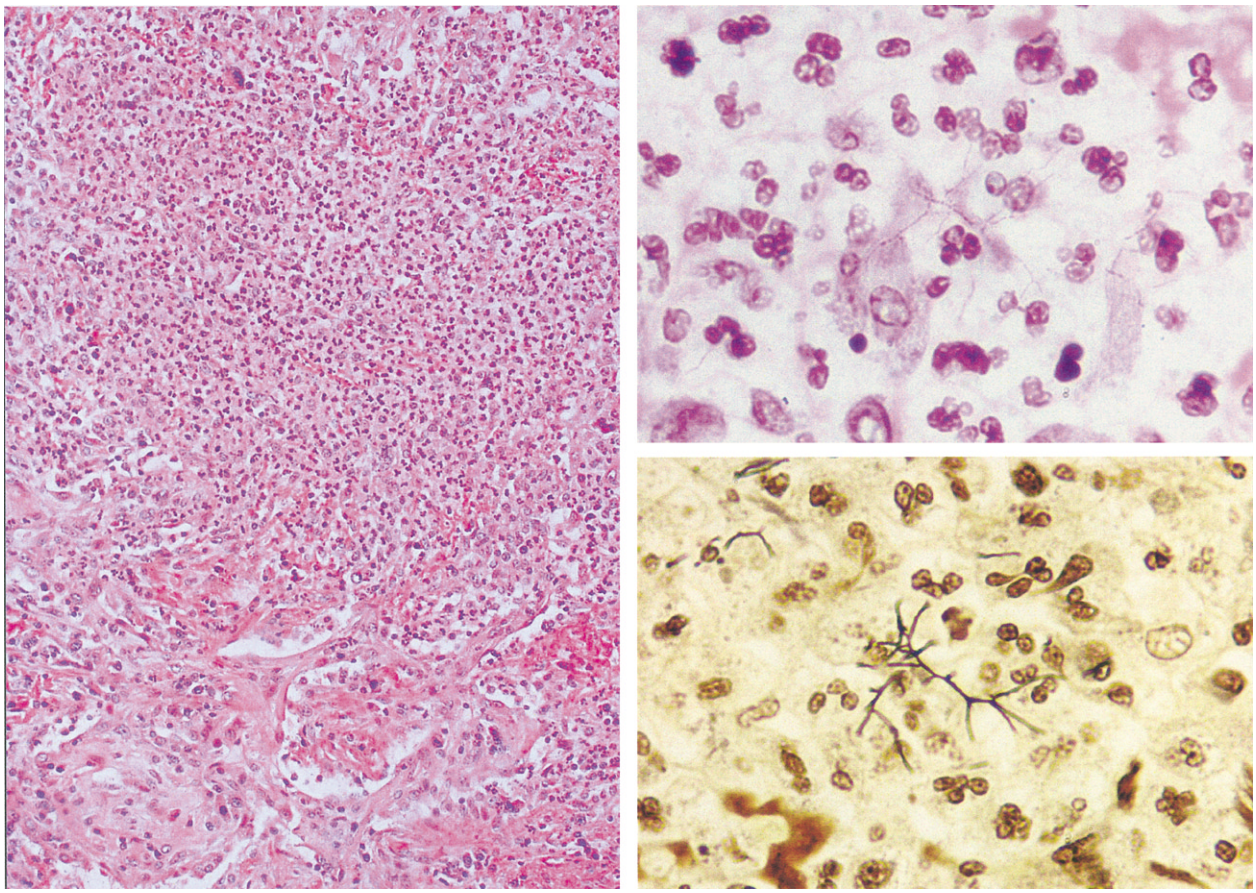

Fig. 1. Pulmonary nocardiosis. An H & E section from video-assisted thoracoscopic lung biopsy from patient 17, showing necrotising pneumonia with abscess formation and extensive infiltration by neutrophils (left × 40). The branching, beaded organisms were demonstrable in the Ziehl–Neelsen stain (top right × 100) and Grocott's methenamine silver stain (bottom right × 100). (Courtesy of Dr. A. Mahar, pulmonary histopathologist, Royal Adelaide Hospital).

Table 3. Radiological findings of patients with pulmonary nocardiosis*

Chest radiographs (available for review in 22 patients)		
Non-segmental consolidation:	68%	(15)
Pulmonary nodule(s)	55%	(12)
Solitary pulmonary nodule	32%	(7, with one showing cavitation)
Multiple nodules	23%	(5, with two showing cavitation)
Lobar consolidation:	18%	(4)
Pleural effusion	18%	(4)
CT chest (available for review in 11 patients)		
Pulmonary nodule(s)	64%	(7)
Solitary pulmonary nodule	36%	(4, with one showing cavitation)
Multiple nodules	27%	(3, with two showing cavitation)
Non-segmental consolidation	55%	(6)
Pleural effusion	36%	(4)
Lobar consolidation	9%	(1)
Ground-glass opacities	9%	(1)
Zonal prevalence		
Mid	31%	(5)
Mid/lower	25%	(4)
Upper	25%	(4)
Lower	19%	(3)

*Actual number in parentheses.

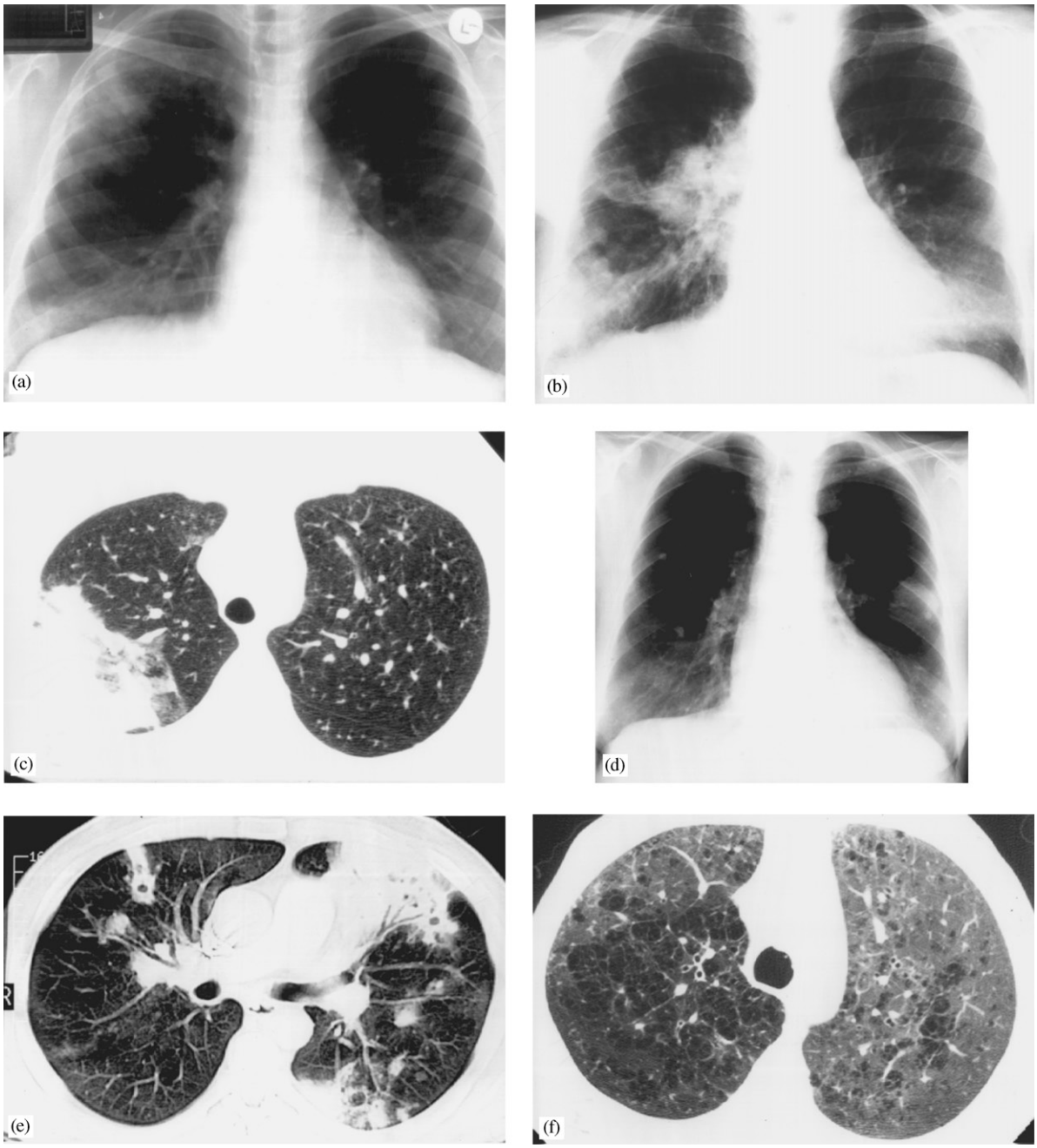

Fig. 2. The diverse radiological manifestations of pulmonary nocardiosis. (a) Chest radiograph: non-segmental air-space consolidation right upper and lower lung zones. (b) Chest radiograph: mass-like consolidation at the right hilum, with multiple nodules and non-segmental consolidation in the right lower lung zone. (c) CT chest: consolidation abutting the pleura. (d) Chest radiograph: SPN; the background of multiple calcified nodules was due to unrelated healed granulomatous disease. (e) CT chest: multiple cavitating pulmonary nodules with consolidation (case 26). (f) CT chest: ground-glass opacity (case 23) is an unusual manifestation of nocardiosis. The abnormalities resolved with anti-*Nocardia* treatment. Background centri-lobular emphysematous change was also noted.

co-pathogens detected, among which fungal species (notably *Aspergillus*) occurred at the highest frequency.

Clinical progress and outcome

Twenty-six patients had received anti-*Nocardia* treatment. Three patients were not given specific treatment because of their palliative status. The detection of nocardiosis was considered to have little clinical significance in two patients (cases 7 and 16) who subsequently showed no evidence of progressive nocardiosis at follow up. Treatment history was not available in the remaining four patients.

Co-trimoxazole was the most popular induction therapy and was given to 21 patients, often over a prolonged

period. Alternative therapy, usually imipenem or a combination of cephalosporin and aminoglycoside, was given to patients with allergy or resistance to co-trimoxazole as suggested by sensitivity studies.

Outcome data was incomplete as a portion of patients were discharged to outpatient care by referring physicians. Broadly speaking, follow-up information in 25 patients had recorded improvement in 14 (56%). Five patients succumbed within the same admission. Six others survived more than 2 months from the diagnosis of pulmonary nocardiosis but died due to their underlying malignancies (in five) or severe COAD (in one).

DISCUSSION

We have provided a descriptive review of a large series of patients with pulmonary nocardiosis and their clinical, microbiological and radiological features at diagnosis. The sporadic occurrence of this pulmonary disease in man is related to inhalation of the sporulated, fragmented nocardial mycelia (2). The bacteria are ubiquitous in the environment in soil, vegetable matter, and are found worldwide. Known pathogenic species to humans include *N. asteroides, N. brasiliensis, N. otitidiscaviarum (N. caviae), N. farcinica, N. nova, N. tranvalensis* and *N. pseudobrasiliensis* (3). *N. asteroides* is by far the commonest pathogen in the nocardial genus and in pulmonary infection of our patients.

In our patient group, the major risk factors for pulmonary nocardiosis were prolonged or high dose corticosteroid treatment, an immuno-suppressed state and underlying respiratory pathology, often co-existing in patients with complex medical problems. Cellular immunity mediated by T-lymphocytes is generally required following phagocytosis for the definitive control and elimination of *Nocardia* (4). Corticosteroids, the backbone of immuno-modulatory or -suppressive therapy, impair the lymphokine response to and phagocytic killing of

Table 4. Species identification of the nocardial isolates.

N. asteroides	15
N. nova	3
N. farcinica	2
N. transvalensis	2
N. otitidiscaviarum (N. Caviae)	1
N. flavonozea	1
Mixed *N. asteroides* + *N. brasiliensis*	1
Unspecified	10

Table 6. Frequency of detection of possible pathogens co-existing with pulmonary nocardiosis.

Aspergillus species	10
Candida species	3
Other fungi (*pencillium, alternaria, paecilomyces* species)	4
Pseudomonas species	4
Non-*pseudomonas* bacteria	5
Other bacteria	
Mycobacteria (M. tuberculosis, M. fortuitum)	2
Legionella longbeachae (by serology)	1
Influenza B	1
Others	
Cytomegalovirus antigenaemia	1
Staphylococcus aureus bacteraemia	1

Table 5. Antimicrobial sensitivity pattern of the nocardial isolates*.

Antibiotics tested	% sensitive isolates		Susceptible to resistant isolates
Ceftriaxone	100	(5/5)	—
Imipenem	90	(9/10)	9:1
Amikacin	86	(6/7)	6:1
Cotrimoxazole	80	(16/20)	4:1
Augmentin	55	(6/11)	6:5
Cefotaxime	50	(2/4)	1:1
Tobramycin	40	(4/10)	2:3
Ciprofloxacin	27	(3/11)	3:7
Minocycline/doxycycline/tetracycline	23	(3/13)	3:10
Gentamycin	20	(1/5)	1:4
Erythromycin	20	(2/10)	1:4
Ampicillin	17	(1/6)	1:5

*Numbers in parentheses are expressed as sensitive strains out of a denominator of the number of isolates tested with that antibiotic. Intermediate susceptibility results were omitted for simplicity.

microbial agents by monocyte-macrophages (5). Not surprisingly therefore, the recently reported cases of pulmonary nocardiosis have been described in AIDS patients with lymphopenia (6–8) or heavily immuno-suppressed individuals (9–19). Our patients were similarly immuno-compromised as a result of either an underlying haemolymphopoietic malignancy or corticosteroid treatment for autoimmune disorders, organ transplants, and other neoplasms. The relative rarity of AIDS in our patients probably reflects the low prevalence of HIV infection in the population examined (700/1.5 million) (20), as well as a possible benefit from co-trimoxazole prophylaxis prescribed to those with low CD4 counts. Nevertheless, the occurrence of nocardiosis in a rare patient with idiopathic CD4 lymphopenia (case 25) is illustrative of the role of T-lymphocytes. Pulmonary nocardiosis in immuno-competent patients with COAD is also increasingly recognized (6, 21–23). A broad range of pulmonary pathology encompassing anatomical, infective, neoplastic, vasculitic, and functional defects was encountered in our patients.

As illustrated by our patients, the risk factors for pulmonary nocardiosis that encourage the invasion by nocardia are synergistic. While nearly all our patients were either immuno-compromised or had underlying pulmonary pathology, it should be noted that two symptomatic patients were previously well (24). Conversely, there were patients in whom the identification of *Nocardia* was regarded as insignificant colonisation. This highlights the difficulty sometimes of deciphering *Nocardia* in respiratory specimens as 'opportunistic' invaders or innocent colonisers, when *Nocardia* is rarely a laboratory contaminant.

We found, as have others (25), that the presenting symptoms are usually referable to the respiratory tract with associated constitutional disturbance. Cough is usually productive with no specific sputum colour. Pleuritic chest pain usually reflects pleural invasion from a contiguous pneumonic infection. On the other hand, disseminated extra-pulmonary infection was not common, occurring in less than 10%. Compared to the higher rate of 10–50% that has been previously reported (6,15,25), our lower incidence of metastatic infection may reflect earlier diagnosis or different immunological defects in different settings. A significantly raised C-reactive protein is considered a laboratory hallmark of systemic infection and should prompt a search for infective etiology. Neutrophilia was not reliably present.

The diverse radiological manifestations of pulmonary nocardiosis reflect their ability to cause both suppurative and granulomatous infection (26,27). On chest radiographs, non-segmental consolidation and pulmonary nodule(s) are the commoner manifestations, while pleural effusions are uncommon. Cavitatory nodules or mass lesions have been more commonly described in AIDS patients (28,29) but were not a prominent feature in this series, probably reflecting the lower proportion of AIDS in this study. It is noted however, that our only HIV positive patient also showed a cavitatory lesion (see Fig. 2). On CT chest studies, solitary or multiple pulmonary nodules that reach 3 cm in size and consolidation were commonly seen. Although there is no distinctive CT feature for pulmonary nocardiosis, CT offers better delineation of the location and extent of disease involvement (16,30), and may guide biopsy if required. Our overall findings confirm previous reports (8,16,28). Neither the chest roentgenograms nor CT chest appearances were pathognomonic or specific.

We found that sputum studies permitted the diagnosis in half of the patients and should never be omitted. On the other hand, half of the patients required additional alternative specimens and bronchoscopic lavage (BAL) undoubtedly provides a better yield when performed. A low threshold of performing BAL for immuno-compromised patients with pneumonia when initial investigations are negative or when there is a lack of response to conventional antibacterials requires emphasis. Lung biopsy specimens in this context should always be sent for microbiological studies. Histopathological sections with routine haematoxylin and eosin stain cannot visualise the filamentous bacteria while methenamine-silver preparations may not always identify them. In the microbiology laboratory, the diagnosis of *Nocardia* is suggested when the gram-stained smears show tangled masses of branching bacilli with characteristic 'beaded' staining. One must be aware that *Nocardia* may fragment into coccoid forms and can be partially acid-fast. Therefore, not every acid-fast bacillus is a mycobacteria (31).

Therapeutically, co-trimoxazole is the most popular initial treatment. Susceptibility testing of *Nocardia* isolates and precise species identification facilitate the choice of alternative regimens when patients are allergic to sulphur compounds or when the organisms are resistant. In our locality, parenteral imipenem, ceftriaxone, and amikacin appear to be useful alternatives. The potential of these agents has also been reported previously (18,19,21,22,32), with recent advocate of imipenem–amikacin combination as initial therapy (22). Prolonged treatment of 6–12 months duration is usually recommended to prevent dissemination and recurrence yet the optimal duration for immuno-compromised patients remains uncertain.

Another finding that has not been emphasised previously (11,19) is the high incidence of co-existing microbial agents, such as *Aspergillus* spp. This phenomenon likely reflects the immunodeficiency state or predisposing pathology of the respiratory tract. Whether these are colonisers or co-infective agents may not always be obvious. A mixed growth, however, will limit the diagnostic certainty regarding which organism is contributory to patient symptoms.

Likewise, the significance of *Nocardia* spp. recovered from smears or cultures of respiratory specimens is not

always clear-cut as discussed earlier. Most of our episodes were considered as significant based on the arbitrary designation when anti-*Nocardia* therapy had been given. Traditionally, most clinicians would not disregard their isolation in association with abnormal pulmonary radiology, immuno-suppressed patients, concomitant neurological symptoms and signs, skin abscess without obvious pathogen (33), or repeated positivity from multiple cultures (3,34). Until we have better tools to determine the virulence of *Nocardia* spp., clinicians have to make an imprecise judgement whether to treat cases without obvious high-risk features. This relies on an understanding of the underlying medical disorder, knowledge of previous microbiological results, liaison with a microbiologist, and ultimately, assessment of the overall clinical picture at the bedside.

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